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## (54) Thin Film Coated Tablets

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# THIN FILM COATED TABLETS

This invention relates to film coated tablets of improved swallowability. More particularly, it concerns analgesic tablets having this characteristic and also having improved absorption rates.

Perhaps the most popular unit dosage form for administering pharmaceutically active ingredients is the tablet. Although this is a widely used dosage form, nevertheless for at least some people, swallowability of such tablets presents a problem. This problem was addressed in the U.S. Patent to John et al 4,302,440 in which the patentees sought to improve the swallowability of aspirin tablets. In accordance with this patent, easily swallowed, gastric-disintegrable aspirin tablets are made by thinly coating the aspirin tablet with an aqueous solution of hydroxypropyl methylcellulose (hereinafter referred to as "HPMC") which is then dried.

In investigating the character of these HPMC coated aspirin tablets, Applicants found that the HPMC film on these tablets retards the absorption of the aspirin as compared with the uncoated tablet. This is an obvious disadvantage both from the point of view of the bioavailability of the active ingredient in these tablets and the rate at which the aspirin gets into the bloodstream of the subject.

It has now been that the bioavailability of the active ingredients in thinly coated tablets coated with HPMC may be significantly improved if, in addition to HPMC, there is also included in the coating polyvinyl pyrrolidone (PVP) and ethylcellulose.

It is accordingly an object of an aspect of the present invention to provide a readily swallowable thinly coated tablet containing a pharmaceutically active material wherein the bioavailability of said pharmaceutically active material is improved as compared with other similarly coated tablets.

It is an object of an aspect of the present invention to provide a thinly coated tablet of the aforesaid mentioned type wherein the coating material comprises a combination of HPMC, PVP and ethylcellulose.

It is an object of an aspect of the present invention to provide a process for preparing tablets of the objects of this invention mentioned.

Various aspects of the invention are as follows:

A film coated tablet of improved swallowability and bioavailability and containing at least one pharmaceutically active ingredient, said tablet being thinly coated with a film comprising as film forming agents the combination of hydroxypropyl methylcellulose; ethylcellulose and polyvinyl pyrrolidone; said film coating being sufficiently thin as to be substantially totally disintegrated by the gastric fluids during the time that the tablet is normally in the stomach of the subject after ingestion.

A film coated tablet of improved swallowability and bioavailability containing at least one pharmaceutically active ingredient; said tablet being thinly coated with a film comprising:

(a) as film forming agents the combination of hydroxypropyl methycellulose, ethylcellulose and polyvinyl pyrrolidone;

(b) a surfactant; and

(c) a carbonate salt

said film coating being sufficiently thin as to be substantially totally disintegrated by the gastric fluids during the time that the tablet is normally in the stomach of the subject after ingestion.

A coating solution useful for coating tablets comprising a volatile organic solvent system having dissolved therein based on the total weight of said coating solution:

(a) from about 4% to about 5% of a combination of film forming agents;

(b) from about 0.5% to about 1.0% by weight of surfactant; and

(c) from about 0.5% to about 1.5% of a carbonate salt

said combination of film forming agents comprising hydroxypropyl methylcellulose, ethylcellulose and polyvinyl pyrrolidone.

It is a feature of the tablets of the present invention that they are thinly coated and disintegrable in gastric fluids. They are intended to alleviate the esophageal discomfort encountered by some people in swallowing tablets but not to increase the disintegration time of the tablets in the stomach. The effort is to keep this disintegration time as close to that of the uncoated tablet. In this respect, the purposes of coating the present tablets are quite different from the purposes for which tablets are provided with an enteric coating in prior art processes and products. In the latter cases, the coatings are intended to resist disintegration in the stomach so that the active ingredients do not come into contact with the gastrointestinal mucosa until the tablet enters the intestine. With this purpose in mind, the enteric coatings will be thicker than the thin coatings contemplated by the present invention.

The present invention is applicable to tablets containing any of a wide variety of materials and particularly, to tablets that contain pharmaceutically active ingredients. It has been found to be especially useful in tablets containing analgesics. By way of exemplifying pharmaceutically active ingredients that may be contained in the present

tablets, the following may be mentioned: analgesics (e.g. aspirin, acetaminophen (APAP), magnesium salicylate, salicylamide and sodium salicylate; either with or without adjuvants such as caffeine); antihistamines (e.g. chlorpheniramine maleate and brompheniramine maleate); decongestants (e.g. pseudoephedrine HCl, and phenylpropanolamine HCl); and antitussives (e.g. dextromethphan HBr, and diphenhydramine HCl), etc. The above ingredients may comprise the sole pharmaceutically active agent in the tablet, or may be used in combination with other pharmaceutically active ingredients. In addition, other tablet adjuvants may also form part of the tablets prepared in accordance with this invention. These include such materials as alkalizing agents, bulking agents, lubricants, stabilizers, disintegrants such as corn starch; modified starch such as StaRx-1500® sold by Colorcon, Inc.; Primojel® and Explotab® both sold by Edward Mendell Co., Inc.; lubricants such as magnesium and zinc stearate; stearic acid; talc; silicon fluid, dimethylpolysiloxane fluid 360 Medical Type, sold by Dow Corning Corp.; bulking agents such as microcrystalline cellulose such as Avicel® pH 101; Avicel® pH 105 both sold by FMC Corporation; Elcema® 100, 150 or 250 sold by Degussa Corp., spray dried lactose and dicalcium phosphate; stabilizers or surfactants such as Tween® 20, 60 or 80 sold by Atlas Chemical Corp; sodium lauryl sulfate; anticaking agents such as Cab-O-Sil® sold by Cabot Corp., Syloid® 244 FP sold by Devisen Chemical Inc., Aerosil®, Supernat® 50 S, both sold by Degussa Corp.

The tablets which are to be coated according to the present invention may be prepared in any of a number of ways well known to those skilled in this art. The particular tabletting procedure employed forms no part of the invention with which we are concerned.

As indicated above, the instant tablets are provided with a thin film of a film forming combination of HPMC, PVP and ethylcellulose. The thickness of the film is most conveniently expressed as the percent by weight of the film based on the weight of the uncoated tablet. This may vary somewhat. The only limitation is that the film is sufficiently thin so that it will be readily disintegrable in gastric fluids. Generally, the film will be in the range of from about 0.5% to about 5.0% by weight based on the weight of the uncoated tablet. Optimally, this will be in the range of from about 1% to about 3% on the same weight basis.

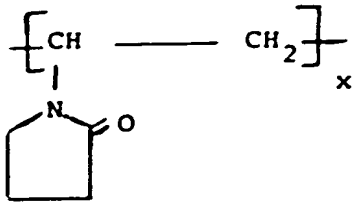
The combined quantity of HPMC, PVP and ethylcellulose that may be contained in film of the tablets of interest may also vary. Usually, this will constitute between about 0.25% to about 2.7% by weight based on the total weight of the uncoated tablet, with the preferred range being from about 0.54% to about 1.62% on the same weight basis.

The relative quantities of the individual film formers may also be present in the film over a range of concentration. Based on the total weight of the uncoated tablet, these ranges on a weight basis may be as follows: HPMC from about 0.09% to about 0.90%; PVP from about 0.09% to about 0.90%; ethylcellulose from about 0.09% to about 0.90%.

HPMC is a propylene glycol ether of methylcellulose. A number of commercial HPMCs are available on the market that can be used in this invention. Among them, mention may be made of Methocel® E (Dow); Methocel® F (Dow); Methocel J (Dow); Methocel® K (Dow); Viscotran® MHPC (Henkel) etc. A material of choice is marketed under the trade designation Methocel® E-15 premium. This is characterized as having a

viscosity of 15 cps at room temperature.

PVP employed herein is a linear polymer of 1-vinyl-pyrrolidone that conforms to the general formula:



where x is the degree of polymerization. This too is available commercially under several trade names. A material that has been found to be especially useful is sold by GAF Corporation under the trade name POVIDONE® K-29-32 having a molecular weight of about 40,000.

Ethylcellulose utilized is an ethyl ether of cellulose. A suitable ethycellulose is marketed by the Dow Chemical Company under the trade designation Ethocel® N-10. This material has a viscosity of about 10 cps.

In certain preferred forms of this invention, it has been found to be advantageous to incorporate a carbonate salt in the films that are deposited on the tablets. This has an advantage in that it serves to facilitate the rupturing of the film on the coated tablet when the latter comes in contact with the acidic gastric fluids. In this fashion, the active ingredients of the tablet become available for absorption into the bloodstream more rapidly. In some instances, the carbonate salt may also serve as an opacifyer for the film.

Any of several carbonate salts may be used for this purpose. By way of illustration, the following may be mentioned: magnesium carbonate; calcium carbonate; sodium carbonate and sodium bicarbonate. However, magnesium carbonate has been

found to be particularly suitable. The carbonate salt will ordinarily comprise about 0.06% to about 0.60% by weight of the uncoated tablet. In a preferred form of this invention, the range will be from about 0.12% to about 0.36% on the same weight basis.

It has also been found useful to incorporate a surfactant in the thin film coating of the present tablets. This serves to solubilize the film and/or the active ingredients in the gastric fluids and therefore, also acts to accelerate the absorption of the active ingredients into the bloodstream. Many well known surfactants may be used for this purpose. These include such materials as sodium lauryl sulfate, Tween 80, Tween 60, Tween 20, Arlacel 20 all sold by Atlas Chemical Co., and dioctylsodiumsulfosuccinate. From among this group, sodium lauryl sulfate has been found to be particularly useful. When present in the instant film coating, the surfactant will comprise from about 0.03% to about 0.30% by weight based on the total weight of the uncoated tablet, with the preferred range being from about 0.06% to about 0.18% on the same weight basis.

The film coated tablets of this invention are prepared by coating the tablets with a solution of HPMC, PVP and ethylcellulose in a volatile solvent system. A number of volatile solvents, alone or in combination with each other, may be used as the principal vehicle. These include such solvents as methylene chloride, methanol, ethyl alcohol and isopropyl alcohol. Good results have been obtained with a solvent system comprising a combination of methylene chloride and methanol.

The volatile solvent system will usually comprise from about 80% to about 95% by weight based on the total weight of film coating solution. In a preferred aspect of this invention, it will constitute between about 85% to about 90%

by weight on the same weight basis.

When the combination of methylene chloride and methanol is used as the solvent system, the major portion of the solvent system will generally be methylene chloride. For the most part, the weight ratio of methylene chloride to methanol will be in the range of from about 50:50 to about 80:20 with the preferred range being from about 60:40 to 70:30.

The combination of film forming agents (i.e. HPMC, PVP and ethylcellulose) will constitute from about 4% to about 5% by weight based on the film coating solution. The content of the individual film forming agents of this combination may vary with HPMC comprising from about 1% to about 3% by weight of the film coating solution, PVP comprising from about 1% to about 3% and ethylcellulose comprising about 1% to about 3% on the same weight basis.

In addition to the above ingredients, one or more surfactants (i.e. the surfactant component) are advantageously included in the film coating solution. Usually, this will comprise from about 0.5% to about 1.0% by weight of the film coating solution. Optimally, this range will be from about 0.6% to about 0.9% on the same weight basis.

As a further ingredient, it is useful to incorporate a carbonate salt in the film coating solution. This may comprise one or more carbonates. As previously indicated, magnesium carbonate is the carbonate of choice. The carbonate component will generally comprise from about 0.5% to about 1.5% by weight of the film coating solution with the preferred range being from about 0.9% to about 1.1% on the same weight basis.

The tablets of the present invention may be coated with film coating solution described above using any of the coating

procedures well known in this art. In one typical procedure, a weighed quantity of uncoated tablets is placed in a coating pan (e.g. Accella Cote Pan).

The following Examples are given to further illustrate the present invention. It is to be understood, however, that the invention is not limited thereto.

## EXAMPLE 1

A. Coating Formulation (CE 1822-31)

| | % by Wt. |
|---|---|
| Methylene chloride | 60.00 |
| Methocel 15 cps (HPMC) | 1.50 |
| Ethocel 10 cps | 1.50 |
| PVP | 1.50 |
| Methanol | 30.00 |
| Sodium lauryl sulfate | 0.50 |
| Magnesium carbonate | 1.00 |
| Propylene glycol | 0.75 |
| Mineral oil, light | 0.25 |
| Tween 80 | 0.25 |
| Opaspray Yellow K-1-2184 | 2.75 |

Methocel 15 cps, Ethocel 10 cps and PVP are first dissolved in methylene chloride. Methanol is added to the mix to complete the solution. Sodium lauryl sulfate, magnesium carbonate, propylene glycol, mineral oil light, Tween 80 and Opaspray Yellow K-1-2184 are mixed together separately to form flurry. It is then added to the polymer solution and thoroughly mixed together.

The tablet core is formed from two adjacent layers. Tablet formulation 87301-68 is a typical core composition. Percentages are based on the weight of the layer.

Layer I:

| | |
|---|---|
| Aspirin (80 mesh) | 84.749 |
| Corn starch | 15.001 |
| Sodium lauryl sulfate (phos. buffered) | 0.250 |

Layer II:

| | |
|---|---|
| Magnesium carbonate (granular) | 44.955 |
| Calcium carbonate (granular) | 39.960 |
| Corn starch (10% aq. paste) | 4.995 |
| Corn starch (dry powder) | 9.590 |
| Castor oil (hydrogenated, powder) | 0.500 |
| Water, deionized QS to 100 | |

The tablets are coated by placing a weighed amount in a coating pan sold by Thomson Engineering Co. under the name Accela-Cote® pan. The temperature of the tablet bed is brought up to 40-45°C. The film coating formulation such as the aforementioned coating formulation CE 1822-31, is sprayed continuously onto the tablets® while the pan is in motion. Spraying is done by the GRECO® Universal Spray Pump sold by Greco, Inc. The vapors are exhausted out of the pan through an exhaust vent.

Sufficient film coating solution is sprayed onto the tablets to achieve a uniform film coat and the tablet weight is increased by 3%. The coating operation is then stopped and the coated tablets are dried in the pan with hot air for about 15 minutes, jogging the pan every few minutes.

A study was conducted to evaluate the effect on the rate of absorption of aspirin (as measured by the total salicylic acid blood levels) from aspirin containing tablets

coated with a coating solution containing HPMC as compared with a coating solution containing HPMC, PVP and ethylcellulose. The respective coatings were applied to an uncoated aspirin tablet coded as Tablet No. 87301-68 and having the foregoing composition.

Using the same procedure two batches of Tablets 87301-68 were respectively coated with coating formulations CE 1637-68 according to the invention and CE 1822-31 as a control. The first one of these formulations is given in the following Table. The second one is the same composition as is given above.

TABLE I

Coating Formulation

CE 1637-68

| | |
|---|---|
| Methylene chloride | 61.275 |
| Methocel 15 cps | 3.375 |
| Methanol | 31.600 |
| Propylene glycol | 0.200 |
| Mineral oil, light | 0.075 |
| Tween 80 | 0.100 |
| Opaspray Yellow K-1-2184 | 3.375 |

Tablets coated with the control coating formula CE 1637-68 (Tablet 1594-42) and tablets coated with the coating formula CE 1822-31 according to the present invention (Tablet 1822-36) were fed to subjects under standardized conditions. Plasma salicylate concentration was determined in blood samples taken from the subjects 10, 20 and 40 minutes after administration of the tablets. Two studies were run, one identified as BC 5-80 and BC 28-80 respectively. In each

of these studies, uncoated aspirin tablets were used as controls. The results of these studies are summarized in Table II below.

TABLE II

Aspirin Bioavailability

| | Geometric Mean Plasma Salicylate Concentration in Blood (μg/ml) | | | | | |
|---|---|---|---|---|---|---|
| | Test No. BC 5-80 | | | Test No. BC-28-80 | | |
| | 10 | 20 | 40 | 10 | 20 | 40 |
| | min | | | min | | |
| Tablet # 87301-68 Uncoated aspirin | 5 | 22 | 47 | 8 | 29 | 52 |
| Control: Tablet # 1595-42 Coating CE 1637-68 | 0 | 1 | 10 | | | |
| Invention: Tablet # CE 1822-36 Coating CE 1822-31 | | | | 2 | 11 | 44 |

As will be apparent from Table II, film coating CE 1822-31 improved early time absorption levels of aspirin (as measured by total salicylic acid) enough to give reasonable levels at 20 minutes and levels equivalent to uncoated aspirin tablets at 40 minutes. In contrast, the tablets with film coating CE 1637-68 (containing only HPMC as the film forming agent) gave significantly lower total salicylic acid levels than

uncoated aspirin at 10, 20 and 40 minutes.

Although the invention has been described with reference to specific forms thereof, it will be understood that many changes and modifications may be made without departing from the spirit of this invention.

WHAT IS CLAIMED IS:

1. A film coated tablet of improved swallowability and bioavailability and containing at least one pharmaceutically active ingredient, said tablet being thinly coated with a film comprising as film forming agents the combination of hydroxypropyl methylcellulose; ethylcellulose and polyvinyl pyrrolidone; said film coating being sufficiently thin as to be substantially totally disintegrated by the gastric fluids during the time that the tablet is normally in the stomach of the subject after ingestion.

2. A film coated tablet according to Claim 1 in which the weight of said film coating is in the range of from about 1% to about 3% by weight based on the total weight of the uncoated tablet.

3. A film coated tablet according to Claim 2 in which the film forming agents are present in film in the following percent ranges based on the weight of the uncoated tablet:

| | | |
|---|---|---|
| (a) | hydroxypropyl methylcellulose | from about 0.09% to about 0.90% |
| (b) | ethylcellulose | from about 0.09% to about 0.90% |
| (c) | polyvinyl pyrrolidone | from about 0.09% to about 0.90% |

4. A tablet according to Claim 1, 2 or 3 in which the pharmaceutically active ingredient comprises an analgesic.

5. A tablet according to Claim 1, 2 or 3 in which said pharmaceutically active ingredient comprises aspirin.

6. A tablet according to Claim 1, 2 or 3 in which said pharmaceutically active ingredient comprises acetaminophen.

7. A film coated tablet of improved swallowability and bioavailability containing at least one pharmaceutically active ingredient; said tablet being thinly coated with a film comprising:

(a) as film forming agents the combination of hydroxypropyl methycellulose, ethylcellulose and polyvinyl pyrrolidone;

(b) a surfactant; and

(c) a carbonate salt

said film coating being sufficiently thin as to be substantially totally disintegrated by the gastric fluids during the time that the tablet is normally in the stomach of the subject after ingestion.

8. A film coated tablet according to Claim 7 in which the weight of said film coating is in the range of from about 1% to about 3% by weight based on the total weight of the uncoated tablet.

9. A film coated tablet according to Claim 8 in which the film forming agents are present in film in the following percent ranges based on the weight of the uncoated tablet:

| | | |
|---|---|---|
| (a) | hydroxypropyl methylcellulose | from about 0.09% to about 0.90% |
| (b) | ethylcellulose | from about 0.09% to about 0.90% |
| (c) | polyvinyl pyrrolidone | from about 0.09% to about 0.90% |

10. A film coated tablet according to Claim 9 in which there is also present in said tablet the following ingredients in the percent ranges listed below based on the weight of the uncoated tablet:

| | | |
|---|---|---|
| (a) | surfactant | from about 0.03% to about 0.30% |
| (b) | carbonate salt | from about 0.06% to about 0.60% |

11. A film coated tablet according to Claim 10 in which said surfactant is sodium lauryl sulfate.

12. A film coated tablet according to Claim 10 in which the carbonate salt is magnesium carbonate.

13. A film coated tablet according to Claim 10 in which said surfactant is sodium lauryl sulfate and said carbonate salt is magnesium carbonate.

14. A tablet according to Claim 7, 8 or 9 in which the pharmaceutically active ingredient comprises an analgesic.

15. A tablet according to Claim 7, 8 or 9 in which said pharmaceutically active ingredient comprises aspirin.

16. A tablet according to Claim 7, 8 or 9 in which said pharmaceutically active ingredient comprises acetaminophen.

17. A coating solution useful for coating tablets comprising a volatile organic solvent system having dissolved therein based on the total weight of said coating solution:

(a) from about 4% to about 5% of a combination of film forming agents;

(b) from about 0.5% to about 1.0% by weight of surfactant; and

(c) from about 0.5% to about 1.5% of a carbonate salt

said combination of film forming agents comprising hydroxypropyl methylcellulose, ethylcellulose and polyvinyl pyrrolidone.

18. A coating solution according to Claim 17 in which said surfactant is sodium lauryl sulfate.

19. A coating solution according to Claim 17 in which the carbonate salt is magnesium carbonate.

20. A coating solution according to Claim 17 in which the surfactant is sodium lauryl sulfate and the carbonate salt is magnesium carbonate.

21. A process for coating tablets which comprises depositing on the surface of said tablets a coating solution of Claim 17, 18 or 19.

22. A tablet according to claim 10, 11 or 12 in which the pharmaceutically active ingredient comprises an analgesic.

23. A tablet according to claim 13 in which the pharmaceutically active ingredient comprises an analgesic.

24. A tablet according to claim 10, 11 or 12 in which said pharmaceutically active ingredient comprises aspirin.

25. A tablet according to claim 13 in which said pharmaceutically active ingredient comprises aspirin.

26. A tablet according to claim 10, 11 or 12 in which said pharmaceutically active ingredient comprises acetaminophen.